

Supporting information:

Total Synthesis of Herboxidiene/GEX 1A

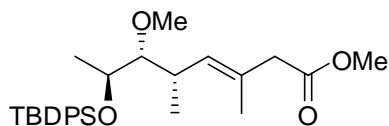
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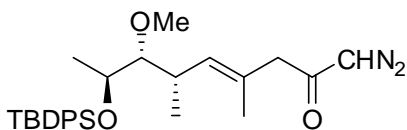
General Information.

All reactions were carried out in oven dried glassware under an argon atmosphere employing standard techniques in handling air-sensitive materials. All solvents were reagent grade. Dichloromethane (DCM) was freshly distilled from calcium hydride, tetrahydrofuran (THF) was freshly distilled from sodium/benzophenone under argon immediately prior to use. Trimethylsilyltrifluoromethanesulfonate (TMSOTf) was freshly distilled before use. All other reagents were used as supplied. Unless otherwise noted, reactions were magnetically stirred and monitored by thin layer chromatography with Sorbent technologies 0.20 mm silica gel 60 plates. Flash chromatography were performed with silica gel 60 (particle size 0.032-0.063 mm) supplied by Sorbent Technologies. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise noted. ^1H NMR spectra were recorded using an internal deuterium lock at ambient temperature on a Varian 400 MHz spectrometer. An internal reference of δ_{H} 7.24 was used for CDCl_3 . Data are presented as follows: chemical shift (in ppm on the δ scale relatively to $\delta_{\text{TMS}} = 0$), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintuplet, m = multiplet, br = broad, ABq = AB quartet, dd = doublet of doublet, dt = doublet of triplet, dq = doublet of quartet), coupling constant (J/Hz) and integration. Resonances that are either partially or fully obscured are denoted obscured (obsc). ^{13}C NMR spectra were recorded on a Varian 400MHz spectrometer. An internal reference of δ_{C} 77.0 was used for CDCl_3 . Infrared spectra were recorded on a Nexus 670 FTIR spectrophotometer. Optical rotations were recorded on an Autopol III digital polarimeter at 589 nm and reported as follows: $[\alpha]_{\text{D}}^{20}$, concentration (c in g/ 100 mL) and solvent. High resolution mass spectra were obtained on a Finnigan MAT-90 spectrometer in the Boston University Mass Spectrometer Laboratory.

Experimental procedures



(3E, 5S, 6S, 7S) 7-(tert-Butyl-diphenyl-silyloxy)-6-methoxy-3,5-dimethyl-oct-3-enoic acid methyl ester (11). A solution of (*S*)-crotylsilane **12** (1.67g, 6.0 mmol) and dimethyl acetal **13**¹ (2.58g, 7.2 mmol) in DCM (12 mL, 0.5 M) was cooled to -78 °C, and TMSOTf (3.48 mL, 18.0 mmol) was charged in. The reaction mixture was slowly warmed up to -50 °C and stirred for 24h before being quenched with saturated NaHCO₃ solution (30 mL) and the aqueous layer was extracted with DCM (3 x 20 mL). The combined organic layers were washed with brine, dried over anhydrous MgSO₄ and concentrated under pressure. Column chromatography on silica gel (2-5% EtOAc/hexane eluant) gave 1.696 g product as a pale yellow oil (62%). ¹H NMR (400 MHz, CDCl₃) δ 7.67 – 7.65 (m, 4H), 7.43 – 7.33 (m, 6H), 4.68 (d, J = 10.4 Hz, 1H), 3.82 (dq, J = 2.8, 6.0 Hz, 1H), 3.57 (s, 3H), 3.53 (s, 3H), 2.88 (dd, J = 2.4, 8.0 Hz, 1H), 2.77 (s, 2H), 2.33 (m, 1H), 1.52 (s, 3H), 1.04 (s, 9H), 1.01 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 6.4 Hz, 3H); ¹³C NMR (400MHz, CDCl₃) δ 172.1, 136.0, 134.5, 132.3, 129.6, 127.5, 89.7, 71.3, 61.2, 51.5, 44.8, 35.3, 27.0, 19.2, 17.1, 16.8, 16.3; IR (Neat) ν_{max} 3000, 2930, 2857, 1739, 1428, 1384, 1259, 1156, 1101, 1044, 933, 822, 772, 740, 702; HRMS (Cl/NH₃) *m/z* calcd for C₂₈H₄₀O₄Si [M+Na]⁺ 491.2594 found 491.2599; [α]_D²⁰ = +21.0 (c 1.1, CHCl₃).

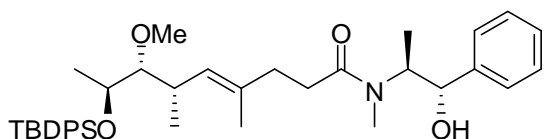


(6S, 7R, 8S, E)-8-(tert-butyl-diphenyl-silyloxy)-1-diazo-7-methoxy-4,6-dimethylnon-4-en-2-one (14). A solution of methyl ester **11** (1.69g, 3.61mmol) in THF-MeOH-H₂O (3:1:1) (14.4 mL, 0.25 M) was added LiOH (303mg, 7.22 mmol) at rt. The heterogeneous reaction mixture was stirred at rt for another 3h before being diluted with diethyl ether 10 mL and careful acidification with 1N HCl solution till PH = 3.0. The aqueous layer was extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous MgSO₄ and concentrated under pressure to give the crude reaction product as viscous pale yellow oil. No further purification needed.

A solution of the crude acid in DCM (18.8 mL, 0.2 M) was treated with the freshly distilled oxalyl chloride (394μL, 4.52 mmol) at rt followed by slow addition of anhydrous DMF (30μL, 0.38 mmol). The reaction mixture was stirred at rt for another 15min before being concentrated under pressure to give a yellow residue. A solution of the crude acid chloride in diethyl ether (4 mL, 1 M) was added into a freshly prepared CH₂N₂ (ca.20 eq.) diethyl ether solution at 0 °C, stirring was maintained at that Temp for 30 min before being quenched with DI H₂O 20 mL. The reaction mixture was allowed to warm to rt and stirred for another 20min until no gas evolution observed. The aqueous layer was extracted with diethyl ether (3 x 20) mL. The combined organic layers were washed with brine, dried over anhydrous MgSO₄ and concentrated under pressure. Column chromatography on silica gel (10% EtOAc/hexane eluant) gave 1.68 g product as bright

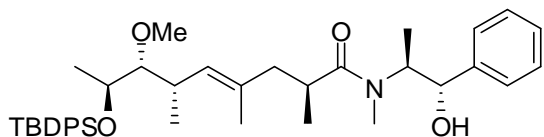
¹ Details of preparation of the corresponding (α)-siloxy aldehyde, see: Smith, N. D.; Kociński, P. J.; Street S. D. A. *Synthesis* **1996**, 652. The aldehyde was then converted to dimethylacetal **13** using TMSOMe and catalytic amounts of TMSOTf in DCM at -50 °C stirring for 12h followed by conventional work-up. This material was used without any further purification.

yellow oil (97% in 2 steps). ^1H NMR (400 MHz, CDCl_3) δ 7.68 – 7.64 (m, 4H), 7.45 – 7.32 (m, 6H), 4.77 (s, 1H), 4.72 (d, $J = 10$ Hz, 1H), 3.82 (dq, $J = 2.0, 6.0$ Hz, 1H), 3.61 (s, 3H), 2.95 (d, $J = 7.2$ Hz, 1H), 2.73 (brs, 2H), 2.33 – 2.26 (m, 1H), 1.47 (s, 3H), 1.04 (s, 9H), 1.00 (d, $J = 6.4$ Hz, 3H), 0.89 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (400MHz, CDCl_3) δ 193.3, 136.0, 135.8, 133.1 129.7, 129.6, 127.5, 89.5, 71.5, 61.2, 52.5, 35.6, 26.9, 19.1, 17.2, 16.8, 16.1; IR (Neat) ν_{max} 3071, 2959, 2932, 2858, 2103, 1643, 1472, 1347, 1102, 1045, 933, 822; HRMS (Cl/NH_3) m/z calcd for $\text{C}_{28}\text{H}_{38}\text{N}_2\text{O}_3\text{Si}$ $[\text{M}+\text{Na}]^+$ 501.2561 found 501.2549; $[\alpha]_{\text{D}}^{20} = +46.3$ °(c 1.8, CHCl_3).



(6S, 7R, 8S, E)-8-(tert-butyl-diphenylsilyloxy)-N-((1S, 2S)-1-hydroxy-1-phenylpropan-2-yl)-7-methoxy-N,4,6-trimethylnon-4-enamide (15). A diazoketone **14** (1.68g, 3.51 mmol) solution

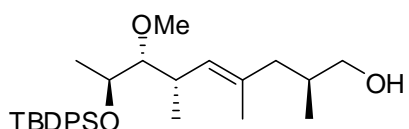
in DCM (70 mL, 0.05 M) was added silver benzoate (804mg, 3.51 mmol) followed by addition of (1S, 2S)-(+)-pseudoephedrine (1.16g, 7.025 mmol). The brown reaction mixture was stirred at rt for 5min before being quenched with H_2O 20 mL. The aqueous layer was extracted with DCM (3X). The combined organic layers were washed with brine, dried over anhydrous MgSO_4 and concentrated under pressure to give a yellow residue. Column chromatography on silica gel (50% EtOAc/hexane eluant) gave 1.73g product as white solid (80%). ^1H NMR (2:1 rotamer ratio, asterisk denotes minor rotamer peaks, 400 MHz, CDCl_3) δ 7.64 – 7.61 (m, 4H) 7.42 – 7.25 (m, 11H), 4.69* (d, $J = 12.8$ Hz, 1H), 4.66 (d, $J = 10.4$ Hz, 1H), 4.57 (t, $J = 7.2$ Hz, 1H), 4.55* (t, $J = 10.4$ Hz, 1H), 4.50 - 4.38 (m, 1H), 4.2 (brs, 1H), 3.93* (quint, $J = 8.4$ Hz, 1H), 3.84 (dq, $J = 2.4, 6.0$ Hz, 1H), 3.59 (s, 3H), 3.57* (s, 3H), 2.92 (dd, $J = 2.4, 8.4$ Hz, 1H), 2.90* (s, 3H), 2.72 (s, 3H), 2.30 – 2.24 (m, 1H), 2.19 – 2.01 (m, 2H), 1.61 (s, OH), 1.47* (s, 3H), 1.44 (s, 3H), 1.09(d, $J = 6.8$ Hz, 3H), 1.04 (s, 9H), 0.97 (d, $J = 6.4$ Hz, 3H), 0.86 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (2:1 rotamer ratio, sterisk denotes minor rotamer peaks, 400MHz, CDCl_3) δ 175.1, 173.8*, 142.4, 140.5*, 135.9, 134.5, 133.9, 133.1, 129.7, 129.5*, 128.7*, 128.4, 127.7, 127.5*, 126.8*, 126.4, 89.8, 76.6, 71.4, 61.1, 58.4, 58.3*, 35.2, 34.6, 33.2, 32.5*, 27.0, 19.2, 17.3, 17.0, 16.2, 15.4*, 14.5; IR (Neat) ν_{max} 2952, 2927, 2867, 1735, 1453, 1434, 1334, 1258, 1190, 1155, 1069, 1028, 1004, 736, 712, 698; HRMS (Cl/NH_3) m/z calcd for $\text{C}_{38}\text{H}_{53}\text{NO}_4\text{Si}$ $[\text{M}+\text{H}]^+$ 616.3822 found 616.3866; $[\alpha]_{\text{D}}^{20} = +46.3$ °(c 1.7, CHCl_3).



(2S, 6S, 7R, 8S, E)-8-(tert-butyl-diphenylsilyloxy)-N-((1S, 2S)-1-hydroxy-1-phenylpropan-2-yl)-7-methoxy-N,2,4,6-tetramethylnon-4-enamide (16). A schlenk flask was charged

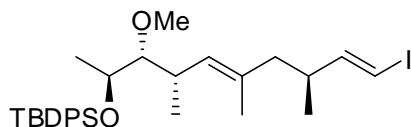
with lithium chloride (331 mg, 7.8 mmol) and was flammable dried under high vacuum. Freshly distilled diisopropylamine (439 μL , 3.13 mmol) and anhydrous THF (0.83 M, 1.57 mL) were added in. n-BuLi (2.50 M in hexanes, 1.17 mL, 2.9 mmol) was charged in at -78 °C. The mixture was warmed up to 0 °C and was stirred at that temperature for 10min. The mixture was cooled back to -78 °C and a solution of amide **15** (803mg, 1.3 mmol) in dry THF (0.19 M, 7 mL) was added very slowly at that Temp. The yellow reaction mixture was stirred at -78 °C for 1h before being warmed up to 0 °C and was

stirred at that Temp for another 45min. MeI (405 μ L, 6.5 mmol, passed though a short column of Al₂O₃ before using) was added slowly into the reaction mixture and stirring was continued at that Temp for 30min before being quenched at 0 °C with saturated NH₄Cl solution. The aqueous layer was extracted with diethyl ether (3X). The combined organic layers were washed with brine, dried over anhydrous MgSO₄ and concentrated under pressure to give a yellow sticky solid (787mg, 96.1% yield). ¹H NMR (2:1 rotamer ratio, asterisk denotes minor rotamer peaks, 400 MHz, CDCl₃) δ 7.67 – 7.64 (m, 4H), 7.42 – 7.31 (m, 11H), 4.71 (d, J = 10.4 Hz, 1H), 4.60 (t, J = 7.2 Hz, 1H), 4.53* (d, J = 8.8 Hz, 1H), 4.18 (brs, 1H), 3.87 (dq, J = 2.4 Hz, 6.0 Hz, 1H), 3.60 (s, 3H), 3.58* (s, 3H), 2.92 (dd, J = 2.4 Hz, 8.8 Hz, 1H), 2.87* (s, 3H), 2.66 (s, 3H), 2.57 – 2.48 (m, 1H), 2.30 – 2.11 (m, 2H), 1.77 (dd, J = 8.0, 13.6 Hz, 1H), 1.43* (s, 3H), 1.42 (s, 3H), 1.16 (d, J = 7.2 Hz, 3H), 1.04 (s, 9H), 0.95(d, J = 6.0 Hz, 3H), 0.86 (d, J = 6.4 Hz, 3H), 0.82* (d, J = 6.0 Hz, 3H), 0.73 (d, J = 6.0 Hz, 3H). ¹³C NMR (2:1 rotamer ratio, sterisk denotes minor rotamer peaks, 400MHz, CDCl₃) δ 178.0, 177.0*, 142.2, 141.9*, 135.6, 134.1, 133.5, 130.9, 129.9*, 129.5*, 129.2, 128.2*, 127.8, 127.3, 126.5*, 125.9, 89.4, 75.8, 74.9, 71.3, 71.2*, 61.9*, 61.0, 57.6, 44.3*, 43.3, 35.3, 35.1*, 34.5*, 34.3, 33.5*, 27.0*, 26.7, 18.9, 17.2, 17.0*, 16.6*, 16.5*, 16.3, 15.4, 15.3*, 14.0; IR (Neat) ν_{\max} 3369, 2963, 2930, 2857, 1618, 1451, 1427, 1381, 1200, 1044, 927, 909, 730, 699, 608; HRMS (Cl/NH₃) m/z calcd for C₃₉H₅₅NO₄Si [M+Na]⁺ 652.3798 found 652.3804; [α]_D²⁰ = +59.1 °(c 1.3, CHCl₃).



(2S, 6S, 7R, 8S, E)-8-(tert-butyl-diphenylsilyloxy)-7-methoxy-2, 4, 6-trimethylnon-4-en-1-ol (17). A schlenk flask was charged with lithium chloride (318 mg, 7.5 mmol) and was flame dried under high vacuum.

Freshly distilled diisopropylamine (736 μ L, 5.25 mmol) and anhydrous THF (0.23 M, 5.4 mL) were added in. n-BuLi (2.50 M in hexanes, 1.95 mL, 4.87 mmol) was charged in at -78 °C. The mixture was warmed up to RT and was stirred at that temperature for another 15min before being cooled back to 0 °C. BH₃ NH₃ complex (90% tech. 171mg, 5 mmol) was added in. The reaction mixture was stirred at 0 °C for 15min before being warmed up to rt and stirred at rt for another 15min. The mixture was cooled back to 0 °C and a solution of methyl amide **16** (787mg, 1.25 mmol, 0.2 M in THF) was added in dropwise. The reaction was allowed to stir at rt for 2h before being quenched with 1N HCl at 0 °C until the pH of aqueous layer was 7.0. The aqueous layer was extracted with diethyl ether (3X). The combined organic layers were washed with brine, dried over anhydrous MgSO₄, and were concentrated under pressure to give a yellow residue. Column chromatography on silica gel (20% EtOAc/hexane eluant) gave viscous pale yellow oil. (496mg, 85%, dr > 10:1). ¹H NMR (400 MHz, CDCl₃) δ 7.67 – 7.64 (m, 4H), 7.42 – 7.33 (m, 6H), 4.63 (d, J = 10 Hz, 1H), 3.89 (dq, J = 2.0 Hz, 6.0 Hz, 1H), 3.60 (s, 3H), 3.40 – 3.28 (m, 2H), 2.92 (dd, J = 2.8, 9.2 Hz), 2.31 – 2.20 (m, 1H), 1.90 (dd, J = 6.8, 13.2 Hz, 1H), 1.68 (m, 1H), 1.57 – 1.52 (m, 1H), 1.43(s, 3H), 1.38 (brs, OH), 1.04 (s, 9H), 0.96 (d, J = 6.4, 3H), 0.86 (d, J = 6.8 Hz, 3H), 0.61 (d, J = 6.4 Hz, 3H); ¹³C NMR (400MHz, CDCl₃) δ 136.0, 134.5, 134.1, 132.7, 129.6, 127.5, 89.9, 71.6, 68.3, 61.3, 44.1, 35.5, 33.6, 27.0, 19.1, 17.6, 16.6, 16.4, 15.8; IR (Neat) ν_{\max} 3355, 3071, 3049, 2957, 2930, 2858, 1472, 1428, 1383, 1103, 1043, 931, 822, 739, 702; HRMS (Cl/NH₃) m/z calcd for C₂₉H₄₄O₃Si [M+Na]⁺ 491.2957 found 491.2981. [α]_D²⁰ = +8.9 °(c 1.1, CHCl₃).

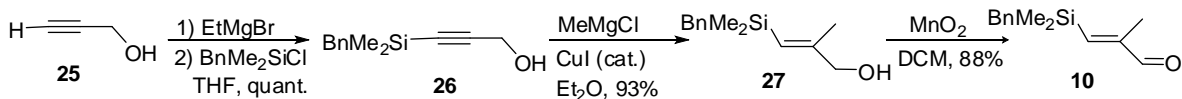


tert-butyl((2*S*, 3*R*, 4*S*, 5*E*, 8*S*, 9*E*)-10-iodo-3-methoxy-4,6,8-trimethyldeca-5,9-dien-2-yloxy)diphenylsilane (8).

A solution of oxalyl chloride (230 μ L, 2.62 mmol) in dry DCM (0.2M, 5 mL) was cooled to -78 $^{\circ}$ C and a solution of DMSO (337 μ L, 4.72 mmol) in 4 mL DCM was charged in. The mixture was stirred at -78 $^{\circ}$ C for 15min before a solution of primary alcohol **17** (490mg, 1.05 mmol) in 3.5 mL DCM was added dropwisely. The reaction mixture was stirred at that temperature for 30min before being quenched with triethyl amine (730 μ L, 5.25 mmol). The reaction mixture was warmed up to 0 $^{\circ}$ C and stirred for another 30min at that temperature before saturated ammonium chloride solution was added into the heterogeneous reaction mixture. The aqueous layer was extracted with diethyl ether (3X). The combined organic layers were combined, washed with brine and concentrated under pressure to give yellow oil as the crude product (quantitative crude yield). The crude aldehyde was used for the next step without further purification. Crude ^1H NMR (400 MHz, CDCl_3) δ 9.50 (d, $J = 1.6$ Hz, 1H), 7.67 – 7.64 (m, 4H), 7.42 – 7.33 (m, 6H), 4.66 (d, $J = 9.6$ Hz, 1H), 3.85 (dd, $J = 2.4, 6.0$ Hz, 1H), 3.60 (s, 3H), 2.92 (dd, $J = 2.4, 8.8$ Hz, 1H), 2.35 – 2.22 (m, 3H), 1.72 (dd, $J = 8.8, 13.6$ Hz, 1H), 1.44 (s, 3H), 1.04 (s, 9H), 0.97 (d, $J = 6.0$ Hz, 3H), 0.86 (d, $J = 6.4$ Hz, 3H), 0.74 (d, $J = 7.2$ Hz, 3H).

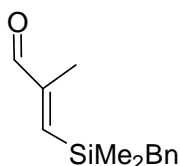
A schlenk flask was charged with CrCl_2 (flammable dried under high vacuum, 886mg, 7.2 mmol) in 7 mL anhydrous dioxane/THF (6:1 mixture). In another flask, the crude aldehyde (1.05 mmol) and CHI_3 (1.06g, 2.7 mmol) was purged with argon three times before 4 mL dioxane/THF (6:1 mixture) was added in. The aldehyde and iodoform solution was transferred into the CrCl_2 solution slowly under argon gas at 0 $^{\circ}$ C. The dark green reaction mixture was covered with aluminum foil and was stirred at rt overnight before being diluted with diethyl ether (5 mL) and quenched at 0 $^{\circ}$ C with water (10 mL). The aqueous layer was extracted with diethyl ether (3X). The organic phases were combined, washed with brine and saturated thiosulfate solution and concentrated under pressure to give a yellow residue. Column chromatography on silica gel (2% EtOAc/hexane eluant) gave the product as clear oil (381mg, 75% yield in 2 steps). ^1H NMR (400 MHz, CDCl_3) δ 7.70 – 7.64 (m, 4H), 7.43 – 7.33 (m, 6H), 6.27 (dd, $J = 8.0, 14.4$ Hz, 1H), 5.76 (d, $J = 14.4$ Hz, 1H), 4.55 (d, $J = 9.6$ Hz, 1H), 3.86 (dd, $J = 2.0, 6.0$ Hz, 1H), 3.61 (s, 3H), 2.92 (dd, $J = 2.4$ Hz, 8.8 Hz, 1H), 2.26 – 2.10 (m, 2H), 1.74 (ABq, $J_{\text{AB}} = 13.8$ Hz, $\Delta\nu = 30.5$ Hz, 1H), 1.72 (ABq, $J = 13.8$ Hz, $\Delta\nu = 30.5$ Hz, 1H), 1.38 (s, 3H), 1.04 (s, 3H), 0.96 (d, $J = 6.4$ Hz, 3H), 0.87 (d, $J = 6.4$ Hz, 3H), 0.70 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (400MHz, CDCl_3) δ 151.7, 135.9, 134.4, 131.6, 129.6, 127.4, 89.8, 73.1, 71.7, 61.3, 46.5, 38.9, 35.5, 27.0, 19.1, 18.8, 17.8, 16.5, 15.8; IR (Neat) ν_{max} 3071, 3049, 2958, 2929, 2857, 1589, 1472, 1427, 1381, 1098, 1042, 931, 821, 738, 698, 608; HRMS (Cl/NH_3) m/z calcd for $\text{C}_{30}\text{H}_{43}\text{IO}_2\text{Si}$ $[\text{M}+\text{Na}]^+$ 613.1975 found 613.1993; $[\alpha]_D^{20} = +12.5^{\circ}$ (c 1.5, CHCl_3).

Preparation of silyl-substituted methacrolein **10**:²



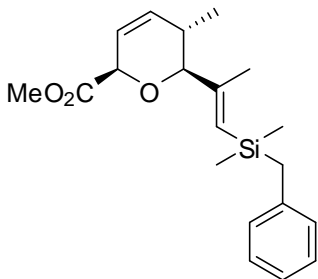
(E)-3-(benzyltrimethylsilyl)-2-methylprop-2-en-1-ol (27).

¹H NMR (400 MHz, CDCl₃) δ 7.21 – 7.17 (m, 2H), 7.07 – 7.03 (m, 1H), 7.00 – 6.98 (m, 2H), 5.47 (s, 1H), 3.99 (d, J = 6.4 Hz, 2H), 2.17 (s, 2H), 1.67 (s, 3H), 0.10 (s, 6H). ¹³C NMR (400MHz, CDCl₃) δ 154.23, 140.0, 128.1, 128.0, 124.0, 68.6, 26.5, 18.4, -2.0; IR (Neat) ν_{max} 3321, 2955, 2896, 1629, 1492, 1451, 1248, 1206, 1152, 1056, 881, 815.



(E)-3-(benzyltrimethylsilyl)-2-methylacrylaldehyde (10). A solution of allylic alcohol **27** (10g, 45 mmol) in DCM (0.3 M, 150 mL) was added pre-activated MnO₂ (58.7g, 675 mmol). The black heterogeneous reaction mixture was stirred at rt for 10 min before being filtered through celite to give a yellow oil as crude product. The crude aldehyde was used without any further purification (8.87g, 89% crude yield).

¹H NMR (400 MHz, CDCl₃) δ 9.18 (s, 1H), 7.04 – 6.98 (m, 2H), 6.90 – 6.86 (m, 1H), 6.79 – 6.78 (m, 2H), 6.43 (s, 1H), 2.05 (s, 2H), 1.58 (s, 3H), 0.00(s, 6H); ¹³C NMR (400MHz, CDCl₃) δ 195.7, 153.0, 151.1, 138.7, 128.3, 124.4, 25.5, 13.5, -2.7; IR (Neat) ν_{max} 3060, 2694, 2897, 3024, 2799, 2956, 1692, 1599, 1493, 1452, 1333, 1250, 1207, 1151, 1057, 1019, 905, 841.7, 794, 763, 699, 629.

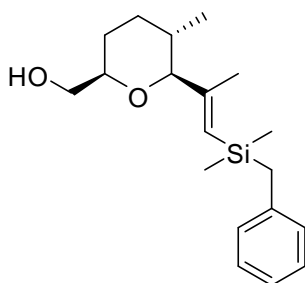


(2R, 5S, 6S)-methyl 6-((E)-1-(benzyltrimethylsilyl)prop-1-en-2-yl)-5-methyl-5,6-dihydro-2H-pyran-2-carboxylate (18).

A solution of crotylsilane **9** (1.94g, 5.5 mmol) and aldehyde **10** (1.33g, 6.1 mmol) in MeCN/DCM (3:1 mixture) (0.05 M, 108 mL) was cooled to -78 °C. Di-*tert*-butyl pyridine (185μL, 0.82 mmol) was charged in at that temperature followed by slow addition of TMSOTf (1.06 mL, 5.5 mmol). The yellow reaction mixture was warmed up to -20 °C and stirred for another 3h before being quenched with saturated NaHCO₃ solution (50mL) at -20 °C and slowly warmed up to RT. The aqueous layer was extracted with diethyl ether (3X). The combined organic layers were washed with brine, dried over anhydrous MgSO₄ and concentrated under pressure to give a brown residue. Column chromatography on silica gel (5% EtOAc/hexane eluant) gave the product as pale yellow oil (1.12g, 65%). (2% EtOAc/hexanes eluent gave unreacted aldehyde 395mg and 20% EtOAc/hexanes gave deprotected crotylsilane 335mg). ¹H NMR (400 MHz, CDCl₃) δ 7.19 - 6.98 (m, 5H), 5.77 (s, 2H), 5.39 (s, 1H), 4.79 (d, J = 3.6 Hz, 1H), 3.74 (s, 3H), 3.52 (d, J = 9.2 Hz, 1H), 2.34 - 2.16 (m, 1H), 2.16 (s, 2H), 1.79 (s, 3H), 0.81 (d, J = 6.8 Hz, 3H), 0.105 (d, J = 7.2 Hz, 3H), 0.097 (d, J = 7.2 Hz, 3H); ¹³C NMR (400MHz, CDCl₃) δ 170.5, 152.2, 140.0, 133.7, 128.2, 126.5, 124.0, 123.1, 88.4, 74.5, 52.3, 31.0, 26.4, 17.0, -

² Detailed experimental procedures for preparation of **26** and **27**, see: (a) Mohamed, M.; Brook, M. A. *Helv. Chim. Acta.* **2002**, 85, 4165. (b) Spino, C.; Gobdout C. *J. Am. Chem. Soc.* **2003**, 125, 12106.

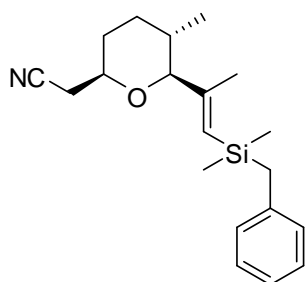
2.0; IR (Neat) ν_{\max} 3059, 3024, 2953, 2927, 2852, 1619, 1600, 1493, 1452, 1378, 1248, 1207, 1155, 1102, 1071, 1017, 833, 699; HRMS (Cl/NH₃) m/z calcd for C₂₀H₂₈O₃Si [M+Na]⁺ 367.1705, found 367.1710; $[\alpha]_D^{20} = -111.2$ (c 1.1, CHCl₃).



((5S)-6-((E)-1-(benzyl dimethylsilyl)prop-1-en-2-yl)-5-methyltetrahydro-2H-pyran-2-yl)methanol (19). A solution of methyl ester **18** (454mg, 1.32 mmol) in diethyl ether (44 mL, 0.03 M) was cooled to 0 °C, LAH (106mg, 2.64 mmol) was charged in. The heterogeneous reaction was stirred at that temperature for 40min before being quenched with 5% HCl solution carefully. The aqueous layer was extracted with diethyl ether (3X). The combined organic layers were washed with

brine, dried over anhydrous MgSO₄, and concentrated under pressure to give viscous clear oil as the crude product. The compound was subjected to the next step without further purification.

A solution of homoallylic alcohol (393mg, 1.24 mmol) in ethanol (12 mL, 0.1 M) was stirred vigorously at RT, chlorotris(triphenylphosphine)rhodium (11mg, 0.12 mmol) was added. The yellow reaction mixture was stirred at rt under H₂ (75psi) before it was checked by crude NMR of the reaction completeness (ca. 16h). The orange reaction mixture was concentrated under pressure to give a dark brown residue. Column chromatography on silica gel (15% EtOAc/hexane eluant) gave the product as viscous pale yellow oil (350mg, 84% in 2 steps). ¹H NMR (400 MHz, CDCl₃) δ 7.19-6.98 (m, 5H), 5.32 (s, 1H), 3.53 (ABq, J_{AB} = 2.0 Hz, $\Delta\nu$ = 27.4 Hz, 2H), 3.31 (d, J 9.2 Hz, 1H), 3.50 - 3.34 (m, 1H), 2.16 (s, 2H), 1.89-1.81 (m, 1H), 1.68 (s, 3H), 1.51 - 1.14 (m, 4H), 0.68 (d, J = 6 Hz, 3H), 0.090 (s, 3H), 0.086 (s, 3H); ¹³C NMR (400MHz, CDCl₃) δ 153.5, 139.9, 128.0, 127.9, 125.4, 123.8, 92.2, 77.6, 66.0, 32.4, 31.9, 27.5, 26.3, 17.6, 16.8, -2.0; IR (Neat) ν_{\max} 3430, 3059, 3024, 2951, 2924, 2850, 1618, 1600, 1493, 1452, 1377, 1247, 1207, 1153, 1107, 1073, 1045, 836, 763, 698; HRMS (Cl/NH₃) m/z calcd for C₁₉H₃₀O₂Si [M+Na]⁺ 341.1913, found 341.1902; $[\alpha]_D^{20} = -3.5$ (c 1.3, CHCl₃).

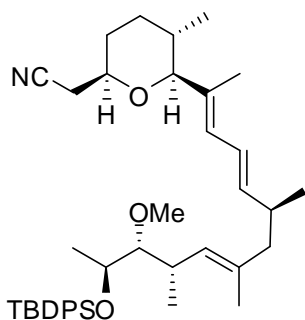


2-((5S)-6-((E)-1-(benzyl dimethylsilyl)prop-1-en-2-yl)-5-methyltetrahydro-2H-pyran-2-yl)acetonitrile (20). A solution of alcohol **19** (268mg, 0.84 mmol) in DCM (2.8 mL, 0.3 M) was stirred at rt. After which pyridine (340 μ L, 4.21 mmol), *p*-toluenesulfonyl chloride (642mg, 3.36 mmol) and DMAP (21mg, 0.17 mmol) were added into the reaction. The homogeneous reaction mixture was stirred at that temperature over night before being quenched with H₂O (2 mL). The

inorganic layer was extracted with diethyl ether (3X). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and concentrated under pressure to give the crude product as yellow oil.

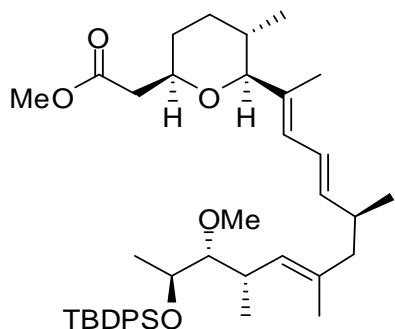
To the crude tosylate product, DMF (0.05 M, 17 mL) and sodium cyanide (206 mg, 4.2 mmol) were added. The yellow reaction mixture was stirred under reflux for 2h before being quenched with water 5 mL at rt. The inorganic layer was extracted with diethyl ether (3X). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and concentrated under pressure to give a yellow residue. Column chromatography on silica gel (10% EtOAc in hexane eluent) gave the product as a pale

yellow oil (66% in 2 steps). ^1H NMR (400 MHz, CDCl_3) δ 7.19 – 6.98 (m, 5H), 5.32 (s, 1H), 3.61 – 3.57 (m, 1H), 3.32 (d, J = 10.0 Hz, 1H), 2.53 (d, J = 5.6 Hz, 2H), 2.16 (s, 2H), 1.90 – 1.85 (m, 1H), 1.76 – 1.72 (m, 1H), 1.69 (s, 3H), 1.47 – 1.44 (m, 2H), 1.26 – 1.18 (m, 2H), 0.68 (d, J = 6.4 Hz, 3H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (400MHz, CDCl_3) δ 153.1, 140.0, 128.2, 128.1, 125.9, 124.0, 117.3, 92.7, 72.1, 31.8, 31.0, 29.6, 26.4, 24.8, 17.5, 16.6, -2.0; IR (Neat) ν_{max} 3080, 3059, 2953, 2927, 2852, 1619, 1600, 1493, 1452, 1378, 1248, 1207, 1155, 1102, 1071, 1017, 833, 699; HRMS (Cl/NH_3) m/z calcd for $\text{C}_{20}\text{H}_{29}\text{NOSi}$ [$\text{M}+\text{Na}$] $^+$ 350.1916, found 350.1927. $[\alpha]_{\text{D}}^{20}$ = -18.8 (c 1.5, CHCl_3).



2-((2*R*,5*S*,6*S*)-6-((2*E*,4*E*,6*S*,8*E*,10*S*,11*R*,12*S*)-12-(tert-butyl)diphenylsilyloxy)-11-methoxy-6,8,10-trimethyltrideca-2,4,8-trien-2-yl)-5-methyltetrahydro-2*H*-pyran-2-yl)acetonitrile (21).

A solution of vinylsilane **20** (71mg, 0.22 mmol) in THF (0.1 M, 2.2 mL) was stirred at 0 °C. TBAF (1.0 M in THF, 0.48 mL) was slowly added into the reaction. The orange reaction mixture was stirred at 0 °C for 5 min and at rt for 10min. The reaction was cooled back to 0 °C and $[\text{AllyPdCl}]_2$ (4 mg, 1 μmol) was added into the reaction mixture followed by slow addition of vinyl iodide **8** (135mg, 0.24 mmol, in 3 mL THF). The reaction was covered with foil and was stirred at rt for 6h. The dark brown reaction was passed through a short column of silicon gel before the solvent was evaporated off to give a dark brown residue. Column chromatography on silicon gel with 2% EtOAc/hexanes recovered part of the unreacted vinyl iodide (50 mg), 8% EtOAc/hexanes removed minor impurities and 10% EtOAc/hexanes gave the product as yellow oil. (72 mg, 51%^{iso}, 64% based on 85% conversion, in cases which were under 30 mg scale of each starting material, isolated yields were around 70% with over 90% conversion of vinyl iodide) ^1H NMR (400 MHz, CDCl_3) δ 7.67 – 7.64 (m, 4H), 7.43 – 7.32 (m, 6H), 6.10 (dd, J = 11.2, 14.4 Hz, 1H), 5.89 (d, J = 11.6 Hz, 1H), 5.49 (dd, J = 7.2, 15.6 Hz, 1H), 4.59 (d, J = 9.6 Hz, 1H), 3.91 (dq, J = 2.4, 6.4 Hz, 1H), 3.60 (s, 3H), 3.65 – 3.56 (m, 1H), 3.32 (d, J = 9.6 Hz, 1H), 2.91 (dd, J = 2.4, 8.8 Hz, 1H), 2.53 (d, J = 5.6 Hz, 2H), 2.28 – 2.15 (m, 2H), 1.92 – 1.87 (m, 2H), 1.79 – 1.73 (m, 1H), 1.70 (s, 3H), 1.65 – 1.60 (m, 1H), 1.50 – 1.46 (m, 1H), 1.40 (s, 3H), 1.27 – 1.19 (m, 2H), 1.00 (s, 9H), 0.95 (d, J = 6.4 Hz, 3H), 0.85 (d, J = 6.4 Hz, 3H), 0.70 (d, J = 6.8 Hz, 3H), 0.64 (d, J = 6.8 Hz, 3H); ^{13}C NMR (400MHz, CDCl_3) δ 141.0, 136.0, 133.6, 129.6, 128.8, 127.5, 127.4, 123.5, 117.3, 90.7, 89.9, 72.3, 71.7, 61.3, 47.4, 35.5, 34.7, 32.0, 31.0, 29.7, 27.0, 24.8, 22.7, 19.4, 17.5, 16.6, 15.8, 14.1, 12.1; IR (Neat) ν_{max} 2956, 2855, 1455, 1427, 1380, 1102, 1069, 966, 932, 822, 702, 610; HRMS (Cl/NH_3) m/z calcd for $\text{C}_{41}\text{H}_{59}\text{NO}_3\text{Si}$ [$\text{M}+\text{Na}$] $^+$ 664.4162, found 664.4116. $[\alpha]_{\text{D}}^{20}$ = -31.5 (c 1.2, CHCl_3); $[\alpha]_{\text{D}}^{20}$ = -22.4 (c 0.5, CHCl_3).



methyl

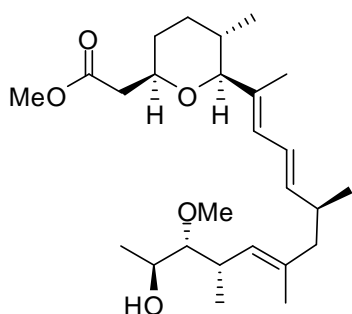
2-((2R,5S,6S)-6-((2E,4E,6S,8E,10S,11R,12S)-12-(tert-butylidiphenylsilyloxy)-11-methoxy-6,8,10-trimethyltrideca-2,4,8-trien-2-yl)-5-methyltetrahydro-2H-pyran-2-yl)acetate (22).

A solution of nitrile (38mg, 0.06 mmol) in dry DCM (0.05 M, 1.2 mL) was cooled to -78 °C. Slowly treated the reaction with fresh DIBAL-H (1.0 M in hexanes, 78µL, 0.078 mmol). The reaction mixture was gradually warmed up to 0 °C (*ca.* 2h) and stirred at 0 °C for another 1h. The reaction was quenched by addition of NaF (13mg, 0.3 mmol) and saturated ammonium chloride soln. (2 mL) at 0 °C after checking the reaction completeness by TLC. Further stirring was continued till the reaction mixture was well separated into two layers. The inorganic layer was extracted with diethyl ether. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and concentrated under pressure to give yellow oil as crude product. The crude aldehyde was immediately used for the next oxidation step without any further purification.

The crude aldehyde (28mg, 0.043 mmol) was dissolved in *t*-butyl alcohol (0.05 M, 1 mL). The mixture was cooled to 0 °C and 2-methyl butene was added quickly into the reaction followed by slow addition of freshly prepared NaClO₂-NaH₂PO₄-H₂O (1g-1g-10 mL) solution (1 mL). The yellow reaction mixture was stirred at rt for 3h before being concentrated under pressure. The residue was diluted with diethyl ether water (*ca.* 1 mL each). The inorganic layer was acidified with 1N HCl till PH = 4.0. The inorganic layer was extracted with diethyl ether (3X). The combined organic layers were dried over anhydrous Magnesium sulfate and concentrated under pressure to give cloudy oil as the crude product. The crude acid was used for the next methylation step without any further purification.

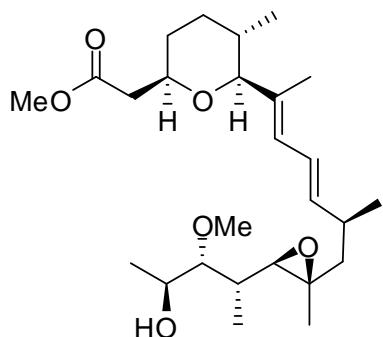
The crude acid (28mg, 0.043 mmol) was dissolved in dry benzene (0.02 M, 3 mL). Anhydrous methanol (200µL) was added followed by slowly addition of TMSCHN₂ (2.0 M in hexanes, 32µL, 65 µmol). The reaction mixture was stirred at rt for 15min before being quenched with water (2 mL). The inorganic layer was extracted with diethyl ether (3X). The combined organic layers were washed with brine and concentrated under pressure to give pale yellow oil as the crude product. Column chromatography on silica gel (10% EtOAc/hexanes eluent) gave the product as pale yellow oil (17mg, 59% in 3 steps). ¹H NMR (400 MHz, CDCl₃) δ 7.66 – 7.64 (m, 4H), 7.42 – 7.33 (m, 6H), 6.10 (dd, J = 10.8, 14.4 Hz, 1H), 5.87 (d, J = 10.8 Hz, 1H), 5.46 (dd, J = 7.20, 15.2 Hz, 1H), 5.58 (d, J = 10.0 Hz, 1H), 3.91 (dq, J = 2.0, 6.0Hz, 1H), 3.77 – 3.72 (m, 1H), 3.64 (s, 3H), 3.60 (s, 3H), 3.31 (d, J = 10.0 Hz, 1H), 2.91 (dd, J = 2.4, 8.8 Hz, 1H), 2.58 (dd, J = 6.0, 15.2 Hz, 1H), 2.38 (dd, J = 2.4, 8.8 Hz, 1H), 2.27 – 2.15 (m, 2H), 1.91 – 1.80 (m, 2H), 1.68 (s, 3H), 1.61 – 1.59 (m, 2H), 1.40 (s, 3H), 1.38 – 1.16 (m, 3H), 1.04 (s, 9H), 0.95 (d, J = 6.4 Hz, 3H), 0.85 (d, J = 6.4 Hz, 3H), 0.68 (d, J = 6.4 Hz, 3H), 0.64 (d, J = 6.8 Hz, 3H); ¹³C NMR (400MHz, CDCl₃) δ 171.9, 140.5, 136.0, 134.3, 132.4, 129.6, 129.5, 128.3, 127.5, 123.7, 90.4, 89.9, 73.8, 71.7, 61.4, 51.5, 47.4, 41.3, 35.5, 34.7, 32.2, 31.6, 30.3, 27.0, 19.4, 19.2, 17.7, 17.7, 16.6, 15.8, 12.3; IR (Neat) ν_{max} 3071, 2955, 2928, 2857, 1741, 1455, 1382,

1289, 1197, 1103, 1067, 966, 932, 822; HRMS (Cl/NH₃) m/z calcd for C₄₂H₆₂O₅Si [M+Na]⁺ 697.4264, found 697.4229. [α]_D²⁰ = -18.8 °(c 1.6, CHCl₃).



methyl 2-((2R,5S,6S)-6-((2E,4E,6S,8E,10S,11R,12S)-12-hydroxy-11-methoxy-6,8,10-trimethyltrideca-2,4,8-trien-2-yl)-5-methyltetrahydro-2H-pyran-2-yl)acetate (23) A solution of silyl ether **22** (17mg, 0.025 mmol) in dry THF (0.05 M, 0.5 mL) was treated with TBAF (1.0 M in THF, 0.1 mL, 0.1 mmol) at rt. Further stirring was continued at that Temp for 3 days. The reaction was diluted with diethyl ether 2 mL followed by addition of saturated NH₄Cl solution (2 mL). The inorganic layer was extracted with EtOAc (3X) and the

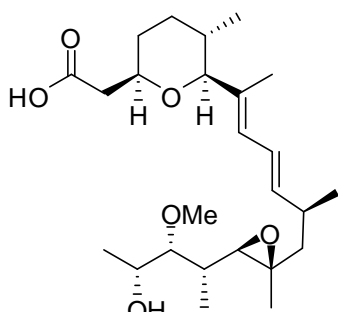
combined organic layers were washed with brine, concentrated under pressure to give a yellow residue. Column chromatography on silica gel (10% EtOAc/hexanes eluent recovered the unconverted starting material; 30% EtOAc/hexanes) gave viscous pale yellow oil as the product (12mg, 81%). ¹H NMR (400 MHz, CDCl₃) δ 6.16 (dd, J = 10.8, 14.8 Hz, 1H), 5.88 (d, J = 10.8 Hz, 1H), 5.50 (dd, J = 6.8, 15.2 Hz, 1H), 4.94 (d, J = 10.0 Hz, 1H), 3.82 – 3.72 (m, 2H), 3.64 (s, 3H), 3.51 (s, 3H), 3.30 (d, J = 9.6 Hz, 1H), 2.92 (dd, J = 3.2, 8.4 Hz, 1H), 2.58 (dd, J = 6.0, 9.6 Hz, 1H), 2.46 – 2.33 (m, 2H), 2.37 (dd, J = 6.8, 14.8 Hz, 1H), 1.99 (dd, J = 6.8, 13.6 Hz, 1H), 1.88 (dd, J = 8.0, 13.6 Hz, 1H), 1.85 – 1.80 (m, 1H), 1.69 (s, 3H), 1.64 (brs, OH), 1.55 (s, 3H), 1.55 – 1.48 (m, 1H), 1.36 – 1.15 (m, 3H), 1.08 (d, J = 6.4 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.4 Hz, 3H), 0.68 (d, J = 6.8 Hz, 3H); ¹³C NMR (400MHz, CDCl₃) δ 171.8, 140.3, 134.3, 132.9, 129.0, 128.3, 124.1, 90.4, 89.5, 73.8, 69.4, 61.5, 51.5, 47.3, 41.2, 35.7, 34.9, 32.3, 32.2, 31.6, 19.9, 17.8, 17.7, 17.1, 16.3, 12.3; IR (Neat) ν_{max} 3470, 2954, 2926, 2870, 1741, 1454, 1379, 1291, 1160, 1198, 1098, 1067, 1019, 966; HRMS (Cl/NH₃) m/z calcd for C₂₆H₄₄O₅ [M+Na]⁺ 459.3086, found 459.3077. [α]_D²⁰ = -53.2 °(c 0.5, CHCl₃).



methyl 2-((2R,5S,6S)-6-((S,2E,4E)-7-((2R,3R)-3-((2R,3R,4S)-4-hydroxy-3-methoxypentan-2-yl)-2-methyloxiran-2-yl)-6-methylhepta-2,4-dien-2-yl)-5-methyltetrahydro-2H-pyran-2-yl)acetate (24) A solution of bis-homoallylic alcohol **23** (10mg, 0.023 mmol) in dry DCM (0.025 M, 1 mL) and MS (4Å) were stirred at 0 °C. The first portion of VO(acac)₂ (0.6mg, 2.26 μmol) was added followed by the addition of *t*-BuOOH (5.5 M in decane, 18 μL) dropwisely. The dark brown reaction was stirred at 0 °C for 12h before a

second portion of VO(acac)₂ (0.6mg, 2.26 μmol) was added followed by slow addition of *t*-BuOOH (5.5 M in decane, 18 μL). The reaction was stirred at that Temp for another 12h before being diluted with DCM (2 mL) and brine (2 mL). The mixture was warmed up to rt and the inorganic phase was extracted with ethyl acetate (3X). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under pressure to give pale yellow residue. Column chromatography on silicon gel (50% EtOAc/hexanes eluent) gave the desired product as pale yellow oil. (4.8mg, 48%, single diastereomer, only in one case, recovered 29% starting material, in all other cases no

starting material or other products were observed). ^1H NMR (400 MHz, CDCl_3) δ 6.21 (dd, $J = 10.4, 14.8$ Hz, 1H), 5.87 (d, $J = 10.0$ Hz, 1H), 5.47 (dd, $J = 8.4, 14.8$ Hz, 1H), 4.00 - 3.92 (m, 1H), 3.77 - 3.71 (m, 1H), 3.64 (s, 3H), 3.49 (s, 3H), 3.29 (d, $J = 10.0$ Hz, 1H), 3.06 (t, $J = 4.8$ Hz, 1H), 2.57 (d, $J = 9.6$ Hz, 1H), 2.56 (dd, $J = 6.8, 15.2$ Hz, 1H), 2.37 (dd, $J = 6.8, 15.2$ Hz, 1H), 2.45 - 2.33 (m, 1H), 1.84 - 1.80 (m, 1H), 1.78 (dd, $J = 5.2, 14.0$ Hz, 1H), 1.69 (s, 3H), 1.69 - 1.64 (m, 1H), 1.60 - 1.46 (m, 2H), 1.36 - 1.15 (m, 3H), 1.26 (s, 3H), 1.19 (d, $J = 6.4$ Hz, 3H), 1.03 (d, $J = 6.4$ Hz, 3H), 0.93 (d, $J = 6.8$ Hz, 3H), 0.68 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (400MHz, CDCl_3) δ 171.8, 139.1, 135.2, 127.6, 125.0, 90.1, 86.7, 73.9, 68.2, 66.1, 61.1, 60.3, 51.5, 46.8, 41.3, 34.9, 34.7, 32.4, 32.4, 31.6, 21.7, 18.9, 17.7, 16.6, 12.7, 11.9; IR (Neat) ν_{max} 3443, 2956, 2925, 2851, 1740, 1456, 1380, 1290, 1198, 1100, 1068, 968, 909; HRMS (Cl/NH_3) m/z calcd for $\text{C}_{26}\text{H}_{44}\text{O}_6$ $[\text{M}+\text{Na}]^+$ 475.3044, found 475.3036. $[\alpha]_{20}^{\text{D}} = -21.7$ °(c 0.5, CHCl_3).



Herboxidiene/GEX 1A (1)

2-((2*R*,5*S*,6*S*)-6-((*S*,2*E*,4*E*)-7-((2*R*,3*R*)-3-((2*R*,3*R*,4*R*)-4-hydroxy-3-methoxypentan-2-yl)-2-methyloxiran-2-yl)-6-methylhepta-2,4-dien-2-yl)-5-methyltetrahydro-2*H*-pyran-2-yl)acetic acid (1). A solution of *S*-alcohol **24** (2.8mg, 6.2 μmol) in dry benzene (0.01 M, 0.5 mL) was added PPh_3 (6.6mg, 0.025 mmol) and *o*-chlorobenzoic acid (3.5mg, 0.022 mmol) followed by slow addition of DIAD (5 μL , 0.025 mmol). The yellow reaction mixture was stirred at rt for 12h before the solvent was removed and gave a cloudy residue. Column

chromatography by 30-50% EtOAc/hexanes gave the desired chlorobenzoic ester along with an inseparable impurity. (6.2mg in total)

A solution of the crude ester (5.6mg, 9.5 μmol) in methanol (0.02 M, 0.55 mL) and water 27 μL was added potassium carbonate (8mg, 0.057 mmol). The reaction mixture was stirred at 40 °C overnight before being cooled down to rt. The clear reaction mixture was then diluted with EtOAc (2 mL) and water (1 mL). The inorganic phase was carefully acidified with 1N HCl till PH = 4.0. The inorganic phase was extracted with EtOAc (3X). The combined organic layers were washed with brine and concentrated under pressure to give a cloudy residue. Column chromatography on silicon gel by 50% EtOAc/hexanes removed impurities and 7% MeOH/DCM eluent gave the natural product as a colorless oil (1.8mg, 66% in 2 steps). ^1H NMR (400 MHz, CD_3OD_3) δ 6.30 (dd, $J = 10.8, 14.8$ Hz, 1H), 5.92 (d, $J = 10.8$ Hz, 1H), 5.50 (dd, $J = 8.8, 14.8$ Hz, 1H), 3.81 (quintet, $J = 6.4$ Hz, 1H), 3.80 - 3.70 (m, 1H), 3.54 (s, 3H), 3.34 (d, $J = 10.0$ Hz, 1H), 2.98 (d, $J = 4.4, 6.4$ Hz, 1H), 2.65 (d, $J = 9.2$ Hz, 1H), 2.46 (dd, $J = 7.2, 15.6$ Hz, 1H), 2.50 - 2.38 (m, 1H), 2.38 (dd, $J = 6.0, 15.6$ Hz, 1H), 1.91 (dd, $J = 4.4, 13.2$ Hz, 1H), 1.90 - 1.82 (m, 1H), 1.70 (s, 3H), 1.74 - 1.65 (m, 1H), 1.60 - 1.43 (m, 1H), 1.29 (s, 3H), 1.40 - 1.22 (m, 1H), 1.26 - 1.18 (m, 1H), 1.11 (d, $J = 6.4$ Hz, 3H), 1.05 (d, $J = 6.4$ Hz, 3H), 0.84 (d, $J = 7.0$ Hz, 3H), 0.70 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (400MHz, CDCl_3) δ 175.1, 42.3, 75.5, 32.8, 33.7, 33.5, 18.0, 91.9, 136.3, 12.6, 129.2, 126.4, 140.5, 36.4, 22.4, 48.0, 62.7, 16.8, 67.8, 36.2, 11.5, 88.6, 69.9, 19.9, 61.9; IR (Neat) ν_{max} 3470, 2962, 2926, 2849, 1724, 1454, 1380, 1099, 1068; HRMS (Cl/NH_3) m/z calcd for $\text{C}_{25}\text{H}_{42}\text{O}_6$ $[\text{M}+\text{Na}]^+$ 461.2879, found 461.2881; $[\alpha]_{20}^{\text{D}} = +4.9$ °(c 0.2, MeOH). ^1H and ^{13}C NMR data for our synthetic herboxidiene/ GEX 1A (**1**) were compared with the natural product in Table 1 and Table

2. The observed significant differences in the C1-C3 region were also reported in Kociński's total synthesis (ref. 5a). This indicated that the data reported for natural herboxidiene was more likely from a carboxylate derivative rather than the free acid.

Table 1. ^1H NMR data for natural and synthetic herboxidiene/GEX 1A (**1**)³

Natural herboxidiene/GEX 1A				Synthetic herboxidiene/GEX 1A		
Position	δ	Multiplicity	J/Hz	δ	Multiplicity	J/Hz
H2 _A	2.45	dd	14.1, 6.6	2.46	dd	15.6, 7.2
H2 _B	2.25	dd	14.1, 7.5	2.38	dd	15.6, 6.0
H3	3.76	m	-	3.80-3.70	m	-
H4 _A	1.86-1.68	m	-	1.90-1.82	m	-
H4 _B	1.30	m	-	1.40-1.22	m	-
H5 _A	1.86-1.68	m	-	1.74-1.65	m	-
H5 _B	1.26-1.12	m	-	1.40-1.22	m	-
H6	1.55	m	-	1.60-1.43	m	-
H6-Me	0.66	d	6.6	0.70	d	6.8
H7	3.34	d	9.9	3.34	d	10.0
H8-Me	1.68	s	-	1.70	s	-
H9	5.90	d	11.1	5.92	d	10.8
H10	6.29	dd	15.0, 10.8	6.30	dd	14.8, 10.8
H11	5.45	dd	15.0, 9.0	5.50	dd	14.8, 8.8
H12	2.44	m	-	2.50-2.38	m	-
H12-Me	1.03	d	6.6	1.05	d	6.4
H13 _A	1.91	dd	13.1, 4.3	1.92	dd	13.2, 4.4
H13 _B	1.26-1.12	m	-	1.26-1.18	m	-
C14-Me	1.27	s	-	1.29	s	-
H15	2.65	d	9.6	2.65	d	9.2
H16	1.45	m	-	1.60-1.43	m	-
C16-Me	0.83	d	6.9	0.83	d	7.0
H17	2.96	dd	6.0, 4.5	2.98	dd	6.4, 4.4
H18	3.78	dq	6.6, 6.3	3.81	quintet	6.4
H19	1.11	d	6.6	1.11	d	6.4
OMe	3.52	s	-	3.52	s	-

Table 2. ^{13}C NMR data for natural and synthetic herboxidiene/GEX 1A (**1**)

Position	Natural δ	Synthetic δ	$\Delta\delta$	Position	Natural δ	Synthetic δ	$\Delta\delta$
C1	179.8	175.1	-4.7	C12	36.5	36.4	-0.1
C2	46.4	42.3	-4.1	C12-Me	22.7	22.5	-0.2
C3	77.0	75.5	-1.5	C13	48.1	48.0	-0.1
C4	33.1	32.8	-0.3	C14	62.6	62.7	+0.1
C5	33.7	33.7	0.0	C14-Me	16.8	16.8	0.0
C6	33.5	33.5	0.0	C15	67.8	67.8	0.0
C6-Me	18.2	18.0	-0.2	C16	36.4	36.3	-0.1
C7	92.2	91.9	-0.3	C16-Me	11.7	11.2	-0.5
C8	136.5	136.3	-0.2	C17	88.6	88.6	0.0
C8-Me	12.1	12.6	+0.5	C18	69.8	69.9	+0.1
C9	129.5	129.2	-0.3	C19	19.9	19.9	0.0
C10	126.6	126.4	-0.2	OMe	61.9	61.9	0.0
C11	140.5	140.5	0.0				

³ ^1H NMR and ^{13}C NMR data for natural herboxidiene/GEX 1A were taken from ref. 5a.

Supporting information:

Total synthesis of Herboxidiene/GEX 1A

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Photocopies of selected ^1H NMR and ^{13}C NMR spectra

All spectra are arranged in the order of their appearance in the manuscript

